Remarks

Claims 1, 4-8, 12-21, 23 and 24 are pending. Claims 6-7 and 14-15 are amended herein. Claims 1, 4-8, 12-21, 23 and 24 were rejected.

No new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 4-8, 12-15 and 23-24 remain rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Jahanshai et al, in view of Binder and further in view of Carruthers et al.

As set forth previously:

Jahanshahi et al. teach that depression in torticollis patients is secondary to the postural abnormality of the head (see page 229, first column), and constitutes "a reaction to the disorder." Botulinium toxin was injected into the superficial neck muscles (not facial muscles) of subjects to treat torticollis (see page 229, second column). The aim of the results presented by Jahanshahi et al. was to assess "improvement of torticollis with botulinum toxin injection accompanied by improvement of depression, reduction of disability, and improvement of the negative body concept and low self esteem" (see page 229, second column). Jahanshahi et al. report that the injection of botulinum toxin into the superficial neck muscles results in straightening of the head and relief from neck pain, and *reduction of depression and disability associated with head position and pain* (page 231, first column). Jahanshahi et al. conclude that the improvement of depression was a "non-specific result" and that it "provides support for the reactive nature of depression and disability in a proportion of torticollis patients" (page 231, second column). Thus, Jahanshahi et al. only suggest the treatment of subject with a skeletal muscular disorder. Contrary to the assertions made in the Office action (see page 5) Jahanshahi et al. simply do not suggest, nor render obvious the selection of any subject without torticollis, let alone the selection and treatment of a subject with dysthymia or major depression.

Binder teaches the reduction of headache pain by injecting botulinum toxin. Binder et al. suggest the extra-muscular injection of botulinum toxin. Binder et al. do not suggest, nor render obvious, the selection and treatment of any subject with dysthymia or major depression.

Caruthers et al. teach the cosmetic use of botulinum toxin to paralyze the depressor anguli oris muscle to alleviate downturn of a subject's mouth. Caruthers et al. teach the cosmetic effect of botulinum toxin. Caruthers et al. do not suggest the use of a toxin to treat any emotional disorder, let alone a depression or dysthymia.

The pending claims are limited methods that include (1) selecting a subject diagnosed with major depression or dysthymia using specific clinical criteria for major depression or dysthymia; and (2) administering to the subject with major depression or dysthymia a therapeutically effective amount of a neurotoxin to a corrugator supercilii or procerus muscle to cause paralysis of the corrugator supercilii or the procerus muscle, thereby decreasing the ability of the subject to frown and treating the major depression or dysthymia in the subject.

Point A: In the Office action (see page 7), it is alleged Jahanshahi et al. teach the alleviation of depression using botullinum toxin. This is incorrect. Jahanshahi et al. teach the use of botullinum toxin to alleviate muscle spasm. The alleviation of muscle spasm and correction of head position results in alleviation of depression. Jahanshahi et al. teach the selection of subject with torticollis. Binder et al. suggest the selection of a subject with a headache. Binder et al. suggest that headaches can be associated with depression. Carruthers et al. teach selecting a subject for cosmetic use of botullinum toxin. However, neither Jahanshahi et al., Binder et al. or Carruthers et al. suggest or render obvious "selecting a subject diagnosed with major depression or dysthymia" as required in the presently pending claims.

The Office action further alleges that it is obvious to combine familiar techniques taught by Jahanshahi et al., Binder et al., and Carruthers et al. However, no evidence is provided to support this assertion. The Examiner has combined one reference on the treatment of muscle spasm (Jahanshahi), one reference on the treatment of headache (Binder et al.), and one reference on cosmetic treatment of the face (Carruthers et al.) In the absence of any factual evidence to the contrary, it appears the Examiner has relied on impermissible hindsight, namely the use of the present specification, to make the present rejection. Even if the combination were made, there is no teaching or suggestion that a subject be selected based on a psychiatric diagnosis (major depression or dysthymia) as opposed to a physical disorder (torticollis or headache). The

proposed combination of references does not yield the claimed invention, hence no prima facie case of obviousness has been made.

Point B: The Examiner discounts the Declaration of Dr. Capehart. The Office action alleges that the claims are not limited to patients that only suffer from major depression or dysthymia as "comprising" is recited in the claimed methods.

As stated above, the claims are directed to methods comprising (1) selecting a subject diagnosed with major depression or dysthymia using specific clinical criteria for major depression or dysthymia; and (2) administering to the subject with major depression or dysthymia a therapeutically effective amount of a neurotoxin to a corrugator supercilii or procerus muscle to cause paralysis of the corrugator supercilii or the procerus muscle, thereby decreasing the ability of the subject to frown and treating the major depression or dysthymia in the subject. Thus, the method must include selecting a subject that has major depression or dysthymia using specific clinical criteria for major depression or dysthymia; the subject does not have a disorder "comprising" major depression or dysthymia. Thus, the Examiner's concern about transitional language is between the preamble and the body of the claim is misplaced.

The Office action alleges that based on the cited prior art, one of skill in the art would be motivated to use botulinum toxin to treat patients suffering from depression. MPEP § 2141 states:

> "[T]he focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge.
>
> Any obviousness rejection should include, either explicitly or implicitly in view of the prior art applied, *an indication of the level of ordinary skill. A finding as to the level of ordinary skill may be used as a partial basis for a resolution of the issue of obviousness.*" (emphasis added).

MPEP § 2145 sets forth that the rebuttal evidence submitted by the Applicants can include evidence of the level of skill of those in the art:

> "Office personnel should consider all rebuttal arguments and evidence presented by applicants. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687. .... It may also

> include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich,* 579 F.2d 86, 91-92, 198 USPQ 210, 214 (CCPA 1978) (Expert opinions regarding the level of skill in the art were probative of the Nonobviousness of the claimed invention.)

However, the Office action discounts the Declaration of Dr. Capehart, a psychiatrist who treats depression, and most certainly is one of skill in the art. Declaration of Dr. Bruce Capehart under 37 C.F.R. § 1.132. In his Declaration, Dr. Capehart confirmed that Jahanshahi et al. does not suggest to a psychiatrist that Botulinum toxin should be used to treat depression in the absence of underlying torticollis. The Office states that if a technique has been used in one method (such as the treatment of torticollis) a person of ordinary skill in the art would recognize that it could be used in other methods in the same way. This is not correct.

Dr. Capehart provided the information that the innervation of the neck is through the spinal root of the accessory nerve (CN XI) and branches of the second and third cervical nerves (C2 and C3). The corrugator supercilii has innervation from a dual nerve supply with contributions from branches of the frontal, zygomatic and buccal branches of the facial nerve. The procerus has innvervation through the buccal branch of the facial nerve. Thus, given a physician's understanding of anatomy and physiology, a psychiatrist, neurologist or any other physician reading Jahanshahi et al. would not predict that injections of Botulinum toxin into the neck to have the same effect as injection of Botulinum toxin into the corrugator supercilli or procerus muscle, *as the innervation is entirely different. This Declaration set forth the scientific basis supporting the assertion that the claimed invention would not be obvious to one of ordinary skill in the art, based on any of the prior art of record.*

The Declaration of Dr. Capehart also confirmed that a psychiatrist would not look to a therapeutic modality for torticollis to treat major depression, nor would they look to headache medications (such as taught by Binder) to provide a route of administration for a psychiatric disorder such as major depression (which has entirely different symptoms and etiology from either a headache or torticollis), nor would they combine these teachings with teachings on cosmetic applications, as taught by Carruthers et al.

Not only does Dr. Capehart's Declaration provide evidence that one of skill in the art would not be motivated to combine the cited prior art , it provides evidence that there is a missing element in the present rejection. Specifically there is nothing in Jahanshahi et al., Binder

et al. or Carruthers et al. that suggests to a one of skill in the art to select a subject that has depression using the accepted clinical characteristics for these diseases, such as would be delineated in the Diagnostic and Statistical Manual of Metal Disorders, 4th edition (DSM-IV) or the Beck Depression Inventory. Neither would one of skill in the art (such as Dr. Capehart) view the combination of references and treat a subject that has major depression using Boluinum toxin by injection into the corrugator supercilii or the procerus muscle.

The Examiner has not provided any rationale as to why the physiological information known to one of skill in the art should be discounted. It was not predictable that injection of a neurotoxin into the corrugator supercilii or the procerus muscle would treat major depression or dysthymia in a subject who was selected based on a diagnosis of specific psychiatric disorders, name major depression or dysthymia.

Point C: Janhanshashi et al. teaches the evaluation of patients with torticollis using the Beck Depression Inventory, which is used to evaluate depressive symptoms in a variety of subjects. The Beck Depression Inventory is a well-known method of evaluating clinical criteria. The Applicants do not claim to have invented this Inventory, nor do they dispute that it has value in classifying many types of subjects. However, the use of this Inventory would not suggest to a psychiatrist to use a therapeutic modality for torticollis to treat major depression, nor would they look to headache medications (such as taught by Binder) to provide a route of administration for a psychiatric disorder such as major depression (which has entirely different symptoms and etiology from either a headache or torticollis), nor would they combine these teachings with teachings on cosmetic applications, as taught by Carruthers et al. This is confirmed in the Declaration of Dr. Capehart, which is discussed above.

Point D: The Office action further disregards the prior Declaration of Dr. Finzi, which provided evidence of the unexpected superior results of the claimed method. The Office action states that it is not clear "where or how this data was obtained" and whether "this data was obtained using the methods disclosed in the instant specification.

The Applicant is unaware of any requirement to provide the location wherein the studies were conducted. Moreover, the Declaration set forth the methods that were used in obtaining the data; it is clear from the original Declaration, which included a full description of the methods,

that the data was obtained using are the presently claimed methods. However, to clarify, a revised Declaration is submitted herewith. This Declaration provides requested confirmation that this data was obtained in the United States using the claimed methods.

The claims are limited to methods for treating depression that include the injection of a neurotoxin into the corrugator supercilii or the procerus muscle. Dr. Finzi compared the effect of the injection of Botulinum into the different muscles of the face for treating depression. *Results are presented in the specification for three patients; these results were obtained using the presently claimed methods in the instant application.* These patients were diagnosed with major depression or intermittent anxiety/depression. Botulinum toxin was administered to the corrugator supercilii or the procerus muscle of each of these subjects using the claimed methods. The injections treated the depression of all of these subjects, who all reported improvements in their mood. Dr. Finzi's Declaration documents that injection of Botulinum toxin into other muscles of the face, such as the lateral orbicularis oculi and the frontalis muscle does not treat depression. The injection of Botulinum toxin into the the corrugator supercilii or the procerus muscle provides an *unexpectedly superior result* for the treatment of depression, as compared to injection of Botulinum toxin into the orbicularis oculi. The showing of the unexpected superior result obtained using the claimed methods overcomes any prima facie case of obviousness.

Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 16-21 remain rejected under 35 U.S.C. 103(a) as allegedly being obvious over Jahanshai et al, in view of Binder, in view of Carruthers et al, and further in view of Wagstaff et al. Applicants respectfully disagree with this rejection.

Jahanshai et al, Binder, and Carruthers et al. are discussed above.

Wagstaff et al. teach that paroxetine (a selective serotonin reuptake inhibitor, SSRI) is effective at treating depression, obsessive-compulsive disorder, and panic disorder. SSRI inhibitors are not used to treat the muscle spasms of torticollis or headaches, and are not used for cosmetic purposes.

The Office action alleges based on the teachings of Wagstaff et al., it is obvious to use SSRI's in combination with botullinum toxin for depression. The Applicant respectfully disagrees.

As noted previously, SSRIs are not used to treat the muscle spasms of torticollis or headaches, and are not used for cosmetic purposes. With regard to torticollis, Kaplan & Sadock's Pocket Handbook of Clinical Psychiatry, Lippincott Williams & Wilkins, 2005, page 418 (see http://books.google.com/books?id=Fwcrfk2BjEsC&pg=PA418&lpg=PA418&dq=SSRI+torticollis&source=web&ots=cqf-4EUG8N&sig=qxCP6l8vNVQQAZG8PNc3utQFJlY&hl=en&sa=X&oi=book_result&resnum=4&ct=result#PPA418,M1, available on the internet) teaches that a side effect of selective serotonin reuptake inhibitors is that they can cause torticollis. Thus Kaplan & Sadock teach away from using SSRI's to treat torticollis, since SSRI's can cause torticollis. The Office action does not address this evidence.

In addition, the Office action does not properly address the evidence provided by Diller et al. (copy previously submitted).

MPEP § 2145 states:

"..a prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness."

In addition, MPEP § 2141.02 states:

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)."

Diller et al., (Fluoxetine-induced extrapyramidal symptoms in an adolescent: a case report, Swiss Med Wkly 2002;132:125–126, copy provided with the prior response) describe a 15-year old girl who developed torticollis "while on flouxetine." The Office action alleges that Diller et al. only teach that fluoxetine (an SSRI) and benztropine cause torticollis. The Office action further alleges that the Diller et al. does not provide evidence that paroxitine (another SSRI inhibitor, which used by Wagstaff et al.) causes torticollis. However, this is incorrect. Diller et al. state that EPS (a syndrome including torticollis) "can and does occur in youth with SSRI. Clinicians should be aware of the SSRIs as a potential causative factor for EPS." *Thus, Diller et al. states that any SSRIs can cause torticollis, this reference is not specific to flouxetine.*

Thus, one of skill in the art would understand Diller et al. to teach away from the use of any SSRI (including paroxitine) in torticollis. This provides substantial evidence that one of skill in the art would not combine the teachings of Jahanshahi et al. with Wagastaff et al.

The claims are limited to methods for treating depression that include the injection of a neurotoxin in to the corrugator supercilii or the procerus muscle. Dr. Finzi compared the effect of the injection of Botulinum into the different muscles of the face for treating depression. *Results are presented in the specification for three patients; these results were obtained using the presently claimed methods in the instant application.* These patients were diagnosed with major depression or intermittent anxiety/depression. Botulinum toxin was administered to the corrugator supercilii or the procerus muscle of each of these subjects using the claimed methods. The injections treated the depression of all of these subjects, who all reported improvements in their mood. Dr. Finzi's Declaration further documents that injection of Botulinum toxin into other muscles of the face, such as the lateral orbicularis oculi and the frontalis muscle does not treat depression. The injection of Botulinum toxin into the corrugator supercilii or the procerus muscle provides an *unexpectedly superior result* for the treatment of depression, as compared to injection of Botulinum toxin into the orbicularis oculi. The subject described in the Declaration was being treated with Sertraline (an SSRI). The demostratin of the unexpected superior results obtained using the claimed methods (presented both in the specification and the Declaration) overcomes any prima facie case of obviousness.

Conclusion

Applicants believe that the present claims are in condition for allowance, which action is requested. *If any issues remain prior to allowance, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview.* It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request. In view of the nature of the rejections, Applicants also expressly reserve the right to file an Appeal.

Respectfully submitted,

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